FORM PTO-1390 (Rev 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: GRIHAC P26AUS

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/423776

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU98/00356	13 May 1998	13 May 1997

TITLE OF INVENTION

METHOD AND APPARATUS FOR MONITORING HAEMODYNAMIC FUNCTION

APPLICANT(S) FOR DO/EO/US

Colin DUNLOP

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ■ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau. (PCT/IB/308 mailed November 19, 1998)
   c. ☐ is not required, as the application was filed in the Untied States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)) is attached.
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ■ An Information Disclosure Statement under 37 CFR 1.97 and 1.98 with PTO FORM 1449.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ■ Other items or information:

■ Preliminary Examination Report	■ Copy of Request
■ Annexes to Pre. Ex. Rep.	■ 6 sheets of formal drawings
■ International Search Report	■ Abstract
☐ German Novelty Search Report	☐ Verified Statement Claiming Small Entity Status
☐ ___ copies of citations	■ Submission of Incomplete Application
■ Form PCT/IB/308	☐ German Language Specification
■ International Publ. No. WO 98/51212 (Face page only)	

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date **November 10, 1999** in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL248837249US addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Michael J. Bujold
(typed or printed name of person mailing paper)

Michael J. Bujold
(signature of person mailing paper)

17. ■ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $840.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)). $760.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	970	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	0	

Claims	Number Filed	Number Extra	Rate		
Total Claim	32 - 20 =	12	x $18.00	216	
Independent Claims	2-3 =	0	x $78.00	0	
Multiple dependent claim(s) (if applicable)			+ $260.00	0	
			TOTAL OF ABOVE CALCULATIONS =	1186	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				0	
			SUBTOTAL =	1186	
Processing fee of $130.00 for furnishing the English translation later the ☐ 20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	0	
			TOTAL NATIONAL FEE =	1186	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	0	
			TOTAL FEES ENCLOSED =	1186	
				Amount to be: refunded	$
				charged	$

a. ■ A check in the amount of $ 1186 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 04-0213 in the amount of $____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-0213. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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11/10/99 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Colin DUNLOP
Serial no.	:	
Filed	:	with an effective filing date of May 13, 1998
For	:	METHOD AND APPARATUS FOR MONITORING HAEMODYNAMIC FUNCTION
Group Art Unit	:	
Examiner	:	
Docket	:	GRIHAC P26AUS

The Commissioner of Patents and Trademarks
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

By way of preliminary amendment, please amend the above identified application as set forth below.

In the Claims:

Please cancel original claims 1-33, as well as all of the Chapter II amended claims, in favor of new claims 34-65 as follows.

34. A method of monitoring haemodynamic function in a human or animal subject, comprising monitoring changes in blood flow in a peripheral blood vessel or tissue bed, to provide an indication of changes in cardiac output.

35. A method in accordance with claim 34, comprising the steps of monitoring relative changes in blood flow, to provide indication of relative changes in cardiac output.

36. A method in accordance with claim 34, wherein the step of monitoring blood flow is carried out non-invasively.

37. A method in accordance with claim 34, wherein the step of monitoring blood flow is carried out continuously.

38. A method in accordance with claim 34, comprising the further step of setting a predetermined limit for blood flow rate, which limit indicates an alarm condition should it be reached.

39. A method in accordance with claim 34, comprising the step of pre-setting a base reference level for blood flow rate being the indicated flow level of the subject at rest before monitoring of the haemodynamic function, or being an average flow level for the particular type of subject prior to monitoring of haemodynamic function.

40. A method in accordance with claim 34, wherein the step of monitoring blood flow includes employing a device which produces a signal which varies with variations in blood flow, and processing the signal to produce an output providing an indication of variations in cardiac output.

41. A method in accordance with claim 40, wherein the step of processing the signal includes the step of modifying the signal by an adjustment factor obtained by a regression analysis of a human or animal subject.

42. A method in accordance with claim 40, wherein the step of processing the signal comprises modifying the signal by an adjustment factor obtained from a co-variate parameter.

43. A method in accordance with claim 42, wherein the co-variate parameter is heart rate.

44. A method in accordance with claim 34, comprising the step of applying the Doppler effect to monitor blood flow.

45. A method in accordance with claim 34, comprising employing an infrared blood flow sensor (e.g. pulse oximeter) to monitor blood flow.

46. A method in accordance with claim 34, comprising employing an electromagnetic flow meter to monitor blood flow.

47. A method in accordance with claim 34, comprising the step of employing a color chart to monitor blood flow, and comparing the color of a predetermined part of the subject's body with the color chart to provide an indication of cardiac output.

48. A method in accordance with claim 34, comprising the step of monitoring the color of a part of the subject's body in order to monitor blood flow.

49. A method in accordance with claim 39, wherein the signal is processed to produce a display which indicates the trend of the cardiac output.

50. A device for monitoring haemodynamic function in a human or animal subject, comprising a blood flow monitor arranged to monitor changes in blood flow in a peripheral vessel or tissue bed, to provide an indication of changes in cardiac output.

51. A device in accordance with claim 50, wherein the blood flow monitor is arranged to monitor relative changes in blood flow, to provide an indication of relative changes in cardiac output.

52. A device in accordance with claim 50, further comprising a processing means for processing a signal from the blood flow monitor to produce an output signal which provides an indication of changes in cardiac output.

53. A device in accordance with claim 52, wherein the processing means is arranged to adjust the signal by an adjustment factor obtained from regression analysis of a human or animal subject.

54. A device in accordance with claim 52, the processing means being arranged to adjust the signal by an adjustment factor obtained from a co-variate.

55. A device in accordance with claim 54, wherein the co-variate input is heart rate.

56. A device in accordance with claim 50, wherein the blood flow monitor comprises a Doppler sensor adapted to monitor blood flow changes.

57. A device in accordance with claim 50, wherein the blood flow monitor comprises an infrared sensor such as a pulse oximeter for monitoring blood flow.

58. A device in accordance with claim 50, wherein the blood flow monitor comprises an electromagnetic flow meter.

59. A device in accordance with claim 52 further comprising a display, wherein the processing means is arranged to control the display to give an indication of changes in the cardiac output in the subject.

60. A device in accordance with claim 59, wherein the device is arranged to display a base reference value to compare with an indicated value during monitoring of haemodynamic function.

61. A device in accordance with claim 59, wherein the device is arranged to display a trend analysis for changes in cardiac output, showing the trend of the changes in cardiac output.

62. A device in accordance with claim 50, wherein the blood flow monitor comprises a color chart can be compared with the color of a predetermined part of the body of the subject.

63. A method in accordance with claim 34, further comprising the step of monitoring a haemodynamic function in a human or animal subject during anaesthesia.

64. A method in accordance with claim 34, further comprising the step of monitoring a haemodynamic function during critical care.

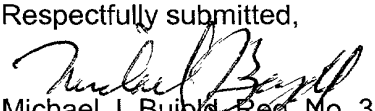
65. A method in accordance with claim 34, further comprising the step of monitoring a haemodynamic function during stress testing.

REMARKS

Please enter the above before consideration of this application. With respect to the above newly entered claims, please note that the subject matter of the Chapter II amended claims is editorially revised and rewritten to bring that subject matter into conformity with the United States claim format.

In the event that there are any fee deficiencies or additional fees are payable, please charge the same or credit any overpayment to our Deposit Account (Account No. 04-0213).

Respectfully submitted,



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ABSTRACT

The present invention relates to a method and apparatus for monitoring haemodynamic function in animals and humans during anaesthesia and surgery. During anaesthesia and surgery the subject's haemodynamic, respiratory, neuromuscular and neurological functions are monitored as indicators of the condition of the health of the subject. Commonly, variations in blood pressure are used to imply corresponding variations in cardiac output, i.e. good blood pressure equals good cardiac output. The present invention utilizes a device to monitor changes of blood flow in peripheral blood vessels of the subject as an indicator of cardiac output. This is believed to provide a much more accurate indicator.

12/17/99 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Colin DUNLOP
Serial no.	:	09/423,776
Filed	:	with an effective filing date of May 13, 1998
For	:	METHOD AND APPARATUS FOR MONITORING HAEMODYNAMIC FUNCTION
Group Art Unit	:	
Examiner	:	
Docket	:	GRIHAC P26AUS

The Commissioner of Patents and Trademarks
Washington, D.C. 20231

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(c-f) and 1.27(b-d))

With respect to the invention described in

- ☐ the specification filed herewith.
- ■ application serial no. 09/423,776 filed with an effective filing date of May 13, 1998.
- ☐ patent no. issued .

I. IDENTIFICATION OF DECLARANT AND RIGHTS AS A SMALL ENTITY

I hereby declare that I am

(a) Independent Inventor

■ a below named independent inventor and that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code to the Patent and Trademark Office.

(b) Non-Inventor Supporting a Claim By Another

☐ making this verified statement to support a claim by for a small entity status for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code and I hereby declare that I would qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under 41(a) and (b) of Title 35, United States Code, if I had made the above identified invention.

(c) Small Business Concern

☐ the owner of the small business concern identified below:
☐ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN _____
ADDRESS OF CONCERN _____

and that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of the Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

(d) Non-Profit Organization

☐ an official empowered to act on behalf of the non-profit organization identified below:

NAME OF ORGANIZATION_____
ADDRESS OF ORGANIZATION_____

TYPE OF ORGANIZATION

☐ UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
☐ TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) AND 501(c)(3))
☐ NON-PROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
(NAME OF STATE_____)
(CITATION OF STATUTE_____)
☐ WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(A) AND 501(C)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA
☐ WOULD QUALIFY AS NON-PROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
(NAME OF STATE_____)
(CITATION OF STATUTE_____)

and that the non-profit organization identified above qualifies as a non-profit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code.

II. OWNERSHIP OF INVENTION BY DECLARANT

I hereby declare that rights under contract or law remain with and/or have been conveyed to the above identified

■ person (item (a) or (b) above)	☐ concern (item (c) above)	☐ organization (item (d) above)

EXCEPT, that if the rights held are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held (1) by any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, (2) any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or (3) a non-profit organization under 37 CFR 1.9(e).

■ no such person, concern, or organization
☐ person, concerns or organizations listed below*

*NOTE *Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities (37 CFR 1.27)*

FULL NAME_____
ADDRESS_____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NON-PROFIT ORGANIZATION

FULL NAME_____
ADDRESS_____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NON-PROFIT ORGANIZATION

III. ACKNOWLEDGMENT OF DUTY TO NOTIFY PTO OR STATUS CHANGE

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

IV. DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing hereon, or any patent to which this verified statement is directed.

V. SIGNATURES COMPLETE ONLY (e) or (f) BELOW

(e)

NOTE: All inventors must sign the verified statement

Colin DUNLOP
Name of Inventor

Signature of Inventor

January 5, 2000
Date

PCT/AU98/00356
Received 06 August 1999

METHOD AND APPARATUS FOR MONITORING HAEMODYNAMIC FUNCTION

The present invention relates to a method and apparatus for monitoring haemodynamic function in humans and animals and, particularly, but not exclusively, to a method and apparatus for monitoring haemodynamic function in humans and animals during anaesthesia and surgery, and its relationship to anaesthetic depth.

During anaesthesia and surgery on a human or animal subject, the subjects haemodynamic respiratory, neuromuscular and neurological functions are monitored as indicators of the condition of the health of the subject as anaesthesia and surgery progress. In general, as anaesthetic (depth) increases, haemodynamic, respiratory and neurological function are depressed or decrease (ie. there is a dose-dependent relationship). During any operation, it is important that adequate perfusion is maintained (ie. oxygenated blood reaches all vital organs including the brain, heart and kidneys). Tissue oxygen delivery is dependent on the level of perfusion or blood flow (cardiac output [CO]) and the amount of oxygen in the arterial blood (Arterial Oxygen Content, CaO_2). Haemodynamic function (causing blood flow to vital organs) is therefore carefully monitored and any changes which indicate that haemodynamic function may not be optimum will alert the anaesthetist who may adjust the anaesthetic dose to compensate ie., to vary the depth of anaesthesia by adjusting anaesthetic depth.

Traditional monitoring of haemodynamic function in anaesthetised patients undergoing surgery, in particular humans, is based on cardiac auscultation, an ECG (electro cardiogram) and blood pressure measurement. Cardiac auscultation will detect the rate of heart beats. The ECG directly monitors cardiac rhythm (electrical rhythm of the heart) and indirectly monitors the pulse rate (assuming the electrical rhythm causes an organised heart muscle contraction). Blood pressure monitoring devices measure

blood pressure, usually measure pulse rate and the information obtained is used by clinicians/anaesthetists to indirectly make inference about (estimate) haemodynamic function, i.e., cardiac output (total blood flow) and organ perfusion. The pulse rate, cardiac rhythm, blood pressure, and inference about haemodynamic functions provide the information necessary to give the anaesthetist an overall picture of haemodynamic function during anaesthesia and surgery.

This type of traditional monitoring of haemodynamic function, in particular the use of blood pressure monitors, is subject to a number of problems.

Indirect blood pressure monitors (systems using a pneumatic cuff and a method to detect the arterial pulse) are inaccurate in small animals, horses and human infants and automated devices can be expensive. Direct blood pressure monitors (systems using a catheter placed in an artery, connected to a pressure measuring device) are accurate but invasive, complex and expensive. Catheterisation of an artery is also NOT done without some risk of complication to the patient.

Further, the general perception in anaesthesia has been that good blood pressure equals good haemodynamic function. That is, if the blood pressure is good, it is taken as an indication that there is adequate blood flow to ensure perfusion of all the vital organs. During anaesthesia and surgery good blood pressure together with good results for the other indicators (cardiac rhythm, pulse rate, etc) has generally been taken to mean that everything is going well for the patient.

The majority of anaesthetic agents depress cardiac output in a dose dependent fashion. Generally, therefore, low blood pressure has been taken to indicate that anaesthetic dose should be lightened and high blood pressure that anaesthetic dose should be increased (although the other indicators also have a bearing on anaesthetic dose and the anaesthetist will take all

indicators into account before deciding on the appropriate action).

The present applicants have realised that blood pressure is not in fact as good an estimator of cardiac output or perfusion during anaesthesia and surgery as has traditionally been considered. Firstly, indirect measurement of blood pressure is inaccurate and secondly it is, in fact, frequently negatively related to total blood flow (cardiac output) and tissue oxygen delivery.

There is a recognised relationship between blood pressure, cardiac output and vascular resistance, as follows:

Cardiac Output = Blood Pressure (MAP-Right Atrial Press) ÷ Vascular Resistance.

One major problem with the usual assumption that blood pressure gives an indication of cardiac output is that none of the usual clinical measurements (auscultation, electrocardiogram, blood pressure) provide any information about vascular resistance.

During surgical procedures at usual anaesthetic levels, it is believed that the subjects body may still experience and respond to painful stimulation, although the subject is not consciously aware of the pain. The body, however, produces its standard sympathetic nervous system response to the painful stimuli, including catecholamine release, resulting in vasoconstriction. The applicants believe that such responses lead to increases in blood pressure during surgery being accompanied by a decrease in cardiac output. This is exactly opposite to the relationship between blood pressure and cardiac output which clinical anaesthetists have traditionally assumed. During painful surgery, therefore, rather than a direct positive relationship between blood pressure and blood flow there is believed to be a variable relationship which may even be in a negative direction.

Given the above observation, and also the fact that non-invasive blood pressure monitors are inherently

inaccurate, it is clear that, in anaesthetised patients undergoing surgery, blood pressure cannot be relied on as an accurate estimator of haemodynamic function.

The present invention provides a method of monitoring haemodynamic function in a human or animal subject, comprising monitoring changes in blood flow in a peripheral blood vessel or tissue bed, to provide an indication of changes in cardiac output.

The method preferably finds most application during anaesthesia and surgery.

It is believed by the applicant that the monitoring of changes in peripheral blood flow will provide a more accurate indication of changes in cardiac output than that inferred from monitoring blood pressure. It is thought that an increase in blood flow in a part of the body is more likely to indicate an increase in cardiac output, as compared to an increase in blood pressure, considering the limitations discussed above relating to using blood pressure as a cardiac output indicator during anaesthesia in surgery.

In anaesthesia and surgery, it is all important that haemodynamic function be maintained such that sufficient oxygenated blood reaches the vital organs, e.g. brain, liver, etc. Good cardiac output is a good indicator of whether there is sufficient blood flow to perfuse the vital organs, particularly during anaesthesia where patients usually breathe high inspired concentrations of oxygen.

Blood flow in an anaesthetised subject may be monitored in a number of ways. Cardiac output can be monitored directly, using indicator dilution techniques such as by the insertion of a pulmonary artery, thermo-dilution, cardiac catheter, for example. This method is intermittent, invasive, requiring cardiac catheterisation, which is not risk free and is not preferred, although insertion of such catheters provides an accurate measurement of total blood flow (cardiac

output). Indirect cardiac output or aortic blood flow measurement may also be made using 2 or 3-dimensional pulsed Doppler cardiac ultrasound, but with computer generated colour flow enhancement display this is very expensive, not accurate, technically difficult and is very sensitive to probe position, movement of the subject or the measuring probe such as occurs during surgical manipulation. In addition it requires a person to continuously hold the transducer on the body in a constant position.

There are a number of devices on the market which the applicant has found could be adapted for monitoring blood flow in blood vessels or tissue beds, non-invasively, relatively inexpensively and generally being relatively non-movement sensitive. Such devices are particularly suitable for monitoring changes in blood flow in peripheral blood vessels, which the applicants believe will still provide a relatively good indication of changes in cardiac output. The method of the present invention is preferably applied by continuously monitoring changes in blood flow, preferably in a peripheral blood vessel, to provide an indication of, changes in cardiac output. For practical clinical application, it is preferred to monitor blood flow in parts of the body where access is easier and, in particular, blood flow in peripheral blood vessels. It may be difficult to measure the actual blood flow in a peripheral blood vessel as, unless an invasive technique is used, the diameter of the peripheral vessel(s) can only be estimated. Changes in blood flow in peripheral vessel(s) can be monitored reliably, however. These changes can be used to estimate changes in cardiac output (total blood flow) we believe, quite reliably. Changes in blood flow in the peripheral vessel during anaesthesia and surgery can, therefore, be utilised by the anaesthetist to adjust dose, eg. if blood flow in the peripheral vessel should fall, then the anaesthetist can imply corresponding falling cardiac output and can reduce

anaesthetic dose to compensate (also taking into account other monitored factors, as discussed above). Changes in blood flow in the peripheral vessel, therefore, give a relative indication of changes in total blood flow (cardiac output).

Blood flow devices are known which detect blood flow in peripheral blood vessels of subjects, by employing an ultrasound sensor which uses the Doppler effect to detect either red blood cell motion or blood vessel wall motion. A signal is produced to simply indicate that motion is occurring (ie. the signal is either on or off/present or absent). An example of such a device is produced by Parks Electronics of Aloha, Oregon, USA. Presently, such a peripheral blood flow monitor is used together with a occlusive cuff and aneroid manometer to indirectly measure blood pressure. The occlusive cuff is tightened to the point that the monitor registers that there is no blood flow in a peripheral artery and the pressure is then read from the manometer. This method only allows the operator to obtain systolic arterial blood pressure. The Doppler monitor is therefore only used in this application to determine whether there is blood flow or whether there is not any blood flow, ie. "on" or "off".

A more advanced continuous wave Doppler device can print a pulsatile wave form based on the frequency and volume of the reflected Doppler, and calculate the peak and mean velocity of the blood flow. Such a device is manufactured by Hiashi Denki Company Limited in Japan (the ES-1000 SPM and ES-1000 SP).

As far as the applicants are aware, no such Doppler monitor has been used for the purpose of monitoring haemodynamic function during anaesthesia. Indeed, none of the prior art devices are suitably adapted to be useful for use in such an application.

The present applicants have utilised a Doppler ultrasound device as a blood flow monitor, to provide a signal whose characteristics preferably varies depending

on the amount of blood flowing in a particular peripheral artery, in order to provide at least a relative indication of changes in total blood flow (cardiac output). This device is used in one preferred embodiment of the method of the present invention.

Pulse oximeters measure the absorption of infra-red radiation by red blood cells in a peripheral vascular bed in order to determine the oxygen saturation of the blood. Since the amount of infra-red radiation absorption depends on the amount of blood, such a device may be adapted, in accordance with an embodiment of the present invention, to provide an indication of relative changes in blood flow in the peripheral vascular bed. This measurement of changes in blood flow may be used as an indication of changes in total blood flow.

In yet a further embodiment, a colour chart may be utilised to estimate changes in blood flow in a tissue bed that has a high density of superficial blood vessels by reference to the colour of the mucous membrane in that tissue bed, eg. gums, tongue, lips, etc. Again, this provides a relative estimate of changes in total blood flow. Colour charts are designed by clinical observation of control subjects under various conditions and relating the observed colour to measurements of blood flow. In the limit, a colour chart is not even necessary to carry out the method of the invention, mere practiced observation of an appropriate tissue bed by a skilled anaesthetist could be used to estimate changes in mucous membrane colour and therefore in blood flow in that area and therefore provide a relative estimate of total blood flow.

The information obtained from monitoring blood flow will be used together with information from an electro cardiogram and measurement of blood pressure to provide a total picture of the haemodynamic condition of a subject during anaesthesia and surgery. This will give sufficient information for the anaesthetist to properly evaluate the haemodynamic condition of the subject and vary anaesthetic

dose accordingly.

Preferably, where a blood flow monitor is used, the method of the present invention includes the further step of applying a regression analysis to the signal produced by the blood flow monitor. Preferably, the regression analysis applied involves the steps of monitoring in an animal or human subject either cardiac output, tissue O_2 delivery (in a subject under anaesthesia breathing a high inspired amount of O_2, arterial oxygen content is generally constant as changes in tissue oxygen delivery reflect changes in cardiac output) against the signal from the blood flow monitor. The data can be used to produce a plot which can be described by regression analysis. The regression equation can be used to calibrate the actual output of the blood flow monitor to provide a more accurate relative indication of CO or tissue oxygen delivery.

Preferably, the method also includes the further step of making a further adjustment to the signal output by the blood flow monitor by applying changes in heart rate as a co-variant factor. This has been found to further improve the estimate of CO of tissue oxygen delivery.

The present invention further provides a device for monitoring haemodyanmic function in a human or animal subject, comprising a blood flow monitor arranged to monitor changes in blood flow in a peripheral vessel or tissue bed, to provide an indication of changes in cardiac output.

Changes in blood flow in a peripheral vessel can preferably be used to provide an indication of changes in cardiac output. By "changes in blood flow" is meant changes of degree, not merely presence or absence of flow.

Preferred blood flow monitors are able to non-invasively monitor blood flow in peripheral blood vessels and provide an output signal who's characteristics vary depending upon actual blood flow in the peripheral vessel(s) being monitored. As discussed above in relation

to the previous aspect of the present invention, changes in blood flow in a peripheral vessel provides a relative indication of changes in total blood flow (cardiac output). Preferably, the device comprises a display or indication means, and means for receiving the signal from the blood flow monitor and processing it to drive a display or other indication means to provide an indication of blood flow, preferably changes in blood flow, which can be monitored by the clinician, such as an anaesthetist.

In a preferred embodiment, the device may be pre-calibrated for a particular subject by, firstly, taking the strength of the blood flow signal from the blood flow monitor when the patient is at rest prior to induction of anaesthesia and surgery and, then using an occlusive cuff to shut off blood flow to the peripheral vessel, obtaining a zero signal. The display on the device can then preferably be set between the upper rest resting blood flow rate and the zero blood flow rate. The device preferably includes an alarm warning indication means to provide an indication of an alarm situation, if the blood flow in the peripheral vessel drops below a certain pre-determined amount.

The device is preferably adapted to give an output which is particularly designed to be useful for an anaesthetist monitoring a subject under surgery. The display preferably provides indications of changes in blood flow in the patient and, preferably, an alarm is provided to sound or provide an indication of an alarm condition when a blood flow change occurs which indicates that a person is either anaesthetised too deeply or not deeply enough. The display may be graded with markings indicating the changes in blood flow in relation to anaesthetic conditions, i.e., too much anaesthetic, too little anaesthetic, etc.

The device is also preferably arranged to apply an adjustment factor to the blood flow monitor signal, the adjustment factor being based on a regression analysis of

actual subjects. The device is also preferably arranged to provide a further adjustment to the signal by taking a co-variant as an input to adjust the signal, and, preferably, the co-variant is heart rate. The adjustment preferably results in an improved output signal.

The blood flow signal may be derived from a pulse oximeter, Doppler monitor, as discussed above.

In an alternative embodiment, the blood flow monitor may comprise a colour chart including coloured patches to be compared with an area of the body of the subject, eg. the lips or tongue. The colour chart would be pre-determined for an "average" subject of the particular animal type (or human being) to give an indication of blood flow depending upon the colour of the body part at the time.

A blood flow monitor and method in accordance with the present invention may have applications other than during anaesthesia. For example, a device which is arranged to monitor changes in blood flow in peripheral vessels or peripheral tissue beds may have application in cardiac stress testing, and other applications.

Features and advantages of the present invention will become apparent from the following description of embodiments thereof, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 is a schematic block diagram of a device in accordance with one embodiment of the present invention;

Figure 2 is a schematic perspective view of a external appearance of a device in accordance with the embodiment of figure 1;

Figure 3 is a view of an example operating display of the device of figure 1, for a human subject during anaesthesia in surgery;

Figures 4 through 7 show various displays of the programming (set up) and alarm setting functions, displayed as for animal operation;

Figure 8 is a view of a "colour chart" in accordance

with an embodiment of the present invention; and

Figure 9 is an example plot of cardiac output or tissue 0_2 delivery against "perfusion index" to demonstrate how regression analysis is to be applied to the output signal of a blood flow monitor in accordance with an embodiment of the present invention.

A device in accordance with an embodiment of the present invention, for use with a method in accordance with the present invention, is illustrated in figures 1 through 7. The device can be used as discussed in the preamble, to monitor changes in blood flow in a peripheral blood vessel of a human or animal subject during anaesthesia and surgery. This gives an indication of relative changes in total blood flow (cardiac output) as one of the indicators for enabling the anaesthetist to monitor the subjects haemodynamic condition and suitably adjust anaesthetic dose. Monitoring peripheral blood flow to provide an indication of changes in cardiac output, as opposed to using blood pressure, runs contrary to anaesthesia practice over the past one hundred years where blood pressure is used in surgery to indicate changes in haemodynamic function or cardiac output. As discussed above, the present applicants believe that, because of responses to painful stimuli during surgery, blood pressure is neither a reliable or positive indicator of changes in cardiac output. They believe that either monitoring of total blood flow or, as in the preferred embodiment of the invention, monitoring of changes in blood flow in a peripheral artery during anaesthesia in surgery, will provide a much better positive indication of relative changes in total cardiac output.

The method of monitoring haemodynamic function during anaesthesia and surgery in accordance with the preferred embodiment of the present invention, also preferably includes the steps of monitoring blood pressure, using standard equipment, monitoring ECG, using standard equipment and monitoring respiration using an airway

thermistor. The heart rate may be monitored using the ECG device. The pulse rate may be monitored using the device in accordance with the present invention, being determined from the peripheral blood flow. These parameters, together with blood flow, provide the total "picture" required by the anaesthetist to enable monitoring and adjustment of anaesthetic dose to ensure the haemodynamic health of the subject.

Figure 1 is a functional block diagram showing components of an ultrasound based device for monitoring blood flow, in accordance with an embodiment of the present invention. The device, generally indicated by reference numeral 1, comprises a Doppler transducer 2 for monitoring blood flow in a peripheral blood vessel of a human or animal subject. In operation, the transducer will be affixed to the appropriate body part of the subject eg. placed distally on the wrist or ankle of a human being, or where an animal is the subject, on the tail. Note that as an alternative to a Doppler transducer 2, a pulse oximeter adapted to monitor blood flow could be used as the blood flow detector (transducer). In fact, any device which is capable of detecting blood flow, in the preferred embodiment in a peripheral vessel, could be used.

Note that a further alternative, in accordance with an alternative embodiment of the present invention, is to use a device such as a pulse oximeter in addition to using the Doppler transducer 2 to monitor the changes in blood flow. The pulse oximeter is, in accordance with this embodiment, adapted to monitor blood volume in a peripheral tissue bed (rather than oxygen saturation which is usually constant during anaesthesia where patients inspire high concentrations of oxygen) and this may be used to improve the estimate of changes in blood flow or to enable estimation of changes in vascular resistance. In this alternative embodiment, the device of figure 1 would also include a sensor and a pulse oximeter device

providing an input about changes in tissue blood volume to the micro computer 4 for processing together with the perfusion input from the Doppler device. The following description, however, relates to an embodiment which employs a Doppler monitor only.

In this embodiment, a continuous wave Doppler driver/receiver 3 is connected to the Doppler transducer for transmitting and receiving ultrasound signals therefrom. A microcomputer and interface 4 is arranged to process the signal from the receiver 3, and drive the LCD display 6 to produce an output indicative of changes in cardiac output (substantially equivalent to tissue oxygen delivery under high inspired concentrations of O_2). It also controls and/or responds to the other peripherals, as follows:

a serial interface 5 to an external printer;

a liquid crystal visual display 6;

a membrane keypad 7;

a control panel 8;

a loud speaker 9; and

a thermistor controller 10 for controlling a airway thermistor (not shown).

Power is provided from the mains via a power supply regulator 11, which is also provided with a back-up rechargeable battery 12, in case of failure of the mains.

In operation, the microcomputer controller 4 operates to process the signal from the Doppler transducer 2 to determine changes in the blood flow rate in the peripheral vessel and to control the liquid crystal display 6 to provide an indication, preferably graphical indication, of the instantaneous relative cardiac output at any time during anaesthesia and surgery. It is preferred to give an output of relative cardiac output, rather than attempting to produce an output indicative of actual cardiac output. Attempting to obtain a measurement giving actual cardiac output is very difficult because a) vessel diameter is required or b) it assumes that changes in

blood flow or vessel diameter in one vessel similarly reflect changes in the whole animal. Monitoring changes in blood flow to provide an output relative to a reference, such as the signal output by the blood flow monitor when the patient is at rest prior to anaesthesia and surgery, is much more convenient, and provides sufficient indication to the anaesthetist to guide him to control anaesthetic depth. The loudspeaker 9 is controlled by the controller 4 to provide an audible pulse signal and alarms should the blood flow fall below or rise above pre-set levels. Preferably, the display 6 also provides a visual alarm indication. The control panel 8 can be used to pre-set the blood flow display and alarm limits, depending upon, for example, the size of the subject and the species of the subject. It is envisaged that a device would be provided suitable for operation on a human subject and a separate device suitable for operation on animal subjects, the animal subject device preferably being adapted for use with a number of animal species, control limits being pre-set for species and animal size by the control panel 8. The microcomputer and interface 4 is arranged to process the Doppler signal output to give an indication of blood flow changes based on the strength of the signal.

Figure 2 shows the external appearance of an example device 1. Equivalent items to figure 1 are given the same reference numerals. The entire device 1 is housed within a robust housing 13. Brackets 14 are provided to hold a reference manual giving operating instructions on the device 1. The device is mounted on rubber feet 15 and has a carrying handle 16. A plug 17 is provided for connection to a mains power supply.

In operation, before a subject is anaesthetised, the Doppler transducer (sensor) 2 is positioned on the skin surface, overlying a peripheral artery such as located in the human forearm at the level of the wrist (radial or ulna artery), on the plantar surface of the foot of a dog

or cat (pedal artery) or on the ventral surface of the tail (coccygeal artery). The device is attached to the subject at rest while conscious and a flow rate determined. The control pad 8 is then used to set a "base line flow" rate and a base bar (reference number 20, figure 3) will appear on the operating display. The base bar will be used as a reference by the anaesthetist as the "normal" flow rate of the conscious resting subject (ie. prior to induction of anaesthesia). As an alternative, the device may also be arranged to store a series of "standard" base bars, being default settings for a particular animal species/size of animal. This would be necessary for animals which may not tolerate attachment of the transducer while conscious. For a human subject, however, it is preferable to pre-set the levels and the display by monitoring of the individual subject.

Figure 3 shows an example operating display for a human subject during anaesthesia and surgery. The left hand side of the display, indicated by reference numeral 21, is taken up by a bar graph which graphically continuously indicates peripheral blood flow rate based on the signal obtained from the peripheral vessel, processed by the controller 4 to provide the display. The base bar 20 is permanently in place on the graphical display and is pre-set by monitoring the flow rate of the conscious subject at rest, prior to the induction of anaesthesia. All flow rates and flow alarms are determined relative to this base bar 20. A high limit bar 22 and low limit bar 23 are also displayed. These can either be pre-set by the anaesthetist or pre-stored in memory to automatically be displayed depending upon the set base bar level and other subject factors, eg. weight, age, etc. For example, appropriate limits could be determined by clinical trials and then stored in the memory of the device.

A moving flow marker 24 is also displayed. This shows the actual real-time flow rate (relative to the base bar). It is this marker 24 that the anaesthetist will

watch carefully to obtain an indication of changes in haemodynamic function. Preferably, the flow marker is arranged to flash. Should the rate fall to the lower limit bar 23 or rise to the high limit bar 22 an audible alarm will sound and the numeric flow display 26 will flash. The anaesthetists attention will thus be drawn to the alarming level of perfusion or blood flow and appropriate action can be taken (eg. altering anaesthetic dose, administration of IV fluid, inotropic drugs etc.). Note that it is unlikely during appropriate levels of anaesthesia during surgery in normal, healthy patients that blood flow will ever rise much above the base bar. This is because standard anaesthetics tend to depress (rather than stimulate) cardiac output in a dose dependent fashion. Such a monitoring device can also be used for monitoring haemodynamic function during critical care such as post cardiac surgery. On this point, a novel device such as this is likely to provide precise clinical data on the effect of anaesthetics and surgical manipulation on peripheral blood flow in humans and animals. However, there are applications of this device, such as cardiac stress testing (treadmill testing) of conscious humans or race horses, where blood flow could increase above the base line measurement.

Referring again to figure 3, the controller 4 also determines the pulse rate of the subject from the Doppler flow signal. This is displayed in the top right hand portion 25 of the display 6. The anaesthetist can also therefore view pulse rate, at a glance. The bottom right hand corner of the display 26 displays the actual (instantaneous) peripheral blood flow rate in alphanumeric.

Should the probe signal change caused by transducer or skin movement relative to the artery or loss of acoustic coupling or otherwise malfunction, a "probe error" display will flash 27.

Switching the device on and taking no further action

defaults the screen to the monitoring display (figure 2). All input and control of the device is set by rotating knob 80 (figure 2) to select function or value and pressing enter to accept function or value.

Upper and lower limit thresholds may also be set for pulse rate, such that if the thresholds are reached audible alarms/visual alarms are provided. A breath to breath audible output and a numeric display of respiratory rate, may also be provided if an airway thermistor is employed.

Figures 4 through 7 show examples of screen displays which may appear during initial set up of the apparatus prior to operation on a human or animal subject. The example screens are based on the device as designed for animal use. This is generally the same as what would appear in the device as designed for human subjects, except that it is envisaged that there would be no screen for default species settings (figure 5) although default settings based on body size could be introduced. Alternatively, all the settings for the alarm function could be entered manually (figure 4). After selecting either the default settings (figure 5) or entering the alarm settings manually (figure 4), the device will then display the result and settings as selected (figure 6) before reverting to the "running" display associated with the continuous monitoring function (a running display is shown in figure 3 for a human being, but a similar display would be shown for animal).

The boxed items of display (figure 4) ("Run", "Pause" etc) are what can be selected by turning the knob 80. A selected function displays as inverse display (ie. white letters on black background). Depressing the knob will then cause the numerical value to increase in magnitude to a maximum number. Subsequently turning the knob by 10° will move the selection to the next boxed item in a left to right, top to bottom flow with wrap-around at bottom. Turning the knob counter clockwise will reverse the

selection highlighting.

Figure 4 shows a typical data entry display for manual entry of the alarm settings, which enables entry of pulse rate high/low limits ie. minimum, base and maximum levels for each item. These values can be set manually based on the preference/clinical experience of the anaesthetist. Alternatively, selection of alarm limits may be based on default settings as shown for animals.

Figure 5 shows a display for default settings which can be selected, which will be based on clinical trials for the particular species/weight of animal (Note that manually five entered default settings may be stored by the user in memory.) Figure 6 illustrates the screen with the default settings which were either entered manually (figure 4) or selected (figure 5). Devices may obviously be designed with different default settings for different species and animal sizes, depending upon application.

Figure 6 is a diagram of the entered/selected alarm setting display, also showing the rest of the control panel from figure 2, incorporating screen selection knob 80, mode button 31, enter button 32 and on/off switch 33.

For this example (10-20kg dog) using figure 6 "enter" can be pressed while the selection knob is set on "Animal Class" to display the Animal Class display from figure 5. A 10-20kg dog will be class "3", the knob is turned 10° clockwise to highlight the numerical animal class function number 3 which results in the various high/low default limits shown in figure 6. Enter button is then pressed which now selects the default settings (for class number 3) and changes the display screen to figure 6. Turning the knob 5° will increment by one value resulting in the display value being 1. Thus turning the knob to approximately 55° clockwise will set the value to 11 (a 15kg dog). The knob can be rotated counter-clockwise to decrement the values. Again the "enter" button is pressed which records and accepts the value. At this point all

the values on the Data Enter display will change to the default values for a 15kg dog. The highlighted box will move to the RUN box assuming the "enter" button will be pressed to accept all the default values and change the display to Figure 7 - If a Run Display of particular value is to be changed, eg. warning tone to OFF, the knob is turned either clockwise or counter-clockwise to the desired box. Pressing enter will toggle the value (to on/off etc) and move the selection to next value (left to right, top to bottom). When all values on the Data Enter display are set and RUN is entered, the display changes to the RUN display.

In the PAUSE mode (Figure 7), the display will be inverse. All Data Enter values will be displayed on the RUN display format.

The Doppler sensor is secured with the animal sedated.

RUN is selected by turning the knob counter-clockwise approximately 10° and "enter" button pressed. The monitor will now start to function, updating the display approximately every 15 seconds, showing heart rate, flow, and moving the flow marker above or below the base value. At any time during operation the knob can be turned to highlight any value on the run display.

During the procedure, the base value may need to be adjusted. Such as with re-positioning the patient for surgery. Turn the knob to highlight the base value eg 2.0 Figure 3, press enter, turn the knob (clockwise or counter-clockwise) to display the desired base flow, then press enter. The monitor will accept the new base flow number and readjust the High/Low limit bars.

With regard to the embodiments discussed above, the output signal from the Doppler transducer is a signal the amplitude and/or frequency of which varies depending upon the rate of blood flow in the peripheral vessel being monitored. As discussed above, the signal can therefore be processed by the micro computer 4 to control a display

to give an output indicative of changes in total blood flow as the changes in blood flow in the peripheral vessel correlate with changes in total cardiac output (CO). In a clinical situation, such as during anaesthesia in surgery, the accuracy of this correlation is important, i.e., it is important that the displayed changes correlate well with the actual changes in cardiac output or tissue oxygen delivery. If the display gives an inaccurate reading, particularly in the critical range (i.e., in the region of the alarm levels) then information given to the anaesthetist can be misleading and ultimately lead to a dangerous situation.

The present applicants have found that the accuracy of the correlation between the changes in the output signal from the Doppler transducer and changes in cardiac output can be much improved by further processing of the signal to adjust the signal by a factor which is based on regression analysis of actual experimental subjects. They have also found that the correlation can be even further improved by adjusting the processed signal by employing a co-variant factor, in the preferred embodiment being heart rate. Adjustment of the signal using these factors preferably leads to a more accurate output and the microprocessor is preferably arranged to process the signal from the Doppler transducer by including adjustments based on these factors.

Figure 9 is a schematic plot of "Perfusion Index" in relation to cardiac output (CO) or tissue oxygen delivery, for a notional experimental subject, to illustrate how regression analysis may be applied in accordance with this embodiment of the invention. Perfusion Index is a term the applicants have chosen to represent the processed output of the Doppler device (or where another device is being used to monitor blood flow, the output from that device). The processed signal from the Doppler device, which is a voltage output proportional to doppler frequency change, whether it be amplitude or frequency,

provides an output known as the Perfusion Index. Ideally, this output will be directly proportional to cardiac output or tissue oxygen delivery (curve A of figure 9). During anaesthesia, high inspired amounts of oxygen are applied so that the arterial oxygen content is relatively constant. Changes in cardiac output can be taken to be substantially the same as changes in tissue oxygen delivery, therefore, in these circumstances.

The ideal, unfortunately, is not the case. From experiments with subjects, however, it is possible to plot Perfusion Index against CO or tissue oxygen delivery, by monitoring cardiac output with another device arranged to directly monitor cardiac output, and by applying a device such as a Doppler monitor to monitor "Perfusion Index", on an experimental subject, to give a realistic plot, plot A in figure 9. The equation for the curve is:

$$y = ax + b$$

where y is in this case cardiac output or tissue oxygen delivery, x is Perfusion Index, a is the slope and b is the intercept (see figure 9).

By adjusting the output of the Doppler device by modifying it by a factor corresponding to a and b, i.e., modifying it by using a regression analysis employing a experimental subject, a more accurate correlation of Perfusion Index (i.e., the new adjusted Perfusion Index) with cardiac output or tissue oxygen delivery can be obtained. In the preferred embodiment, therefore, the micro computer 4 is arranged to modify the output of the Doppler receiver 3 by a factor relating to the regression analysis. This has been found to provide a much improved output, i.e., a more accurate indication of the cardiac output.

In application, therefore, regression analysis is carried out by a monitoring perfusion index against cardiac output or tissue oxygen delivery for a plurality of subjects. The results of the regression analysis are then used to calculate a weighting factor to be applied to

the output from the Doppler monitor, by the device in accordance with the embodiment of the present invention, in order to adjust that output to create a more accurate output indicative of cardiac output or tissue oxygen delivery. In the example given in figure 9, a and b are calculated and y with the new adjusted output, is produced in accordance with the formula $y = ax + b$.

Note that tissue oxygen delivery = tissue blood flow (cardiac output) x arterial oxygen content.

A further improvement to the correlation of Perfusion Index to cardiac output can be made by further modifying the output signal from the Doppler transducer by making an adjustment for a co-variate factor.

Cardiac output = heart rate x stroke volume.

Cardiac output also = mean arterial pressure/vascular resistance.

There are therefore a number of variants which influence cardiac output and which may also determine the accuracy of an output signal from the Doppler monitor. The applicants have found that, in patients anaesthetised for surgery, including a co-variate factor based on heart rate also results in an increase in the accuracy of the final output of the device. A co-variate factor relating to mean arterial pressure does not improve the output and in fact degrades it.

Preferably, therefore, in accordance with the preferred embodiment of the invention, the output of the Doppler monitor is also adjusted by applying a co-variate factor, based on the heart rate of the patient. Again, a number of experimental subjects are monitored to see what variation of the output of the Doppler monitor (perfusion index) occurs with pulse rate. A weighting factor is then applied to the output from the signal in accordance with detected heart rate for a patient, to further improve the response of the device.

A further modification which may be made to the device is to process the output to provide an indication

of the "trend" of the output and also provide a display of the trend. All measurements are stored periodically, for example every one to five seconds, and a display which gives the direction that the output is taking, i.e., either up or down, is provided for the anaesthetist. This "trend" display can be useful in anaesthesia, and will generally provide more direction to an anaesthetist as far as anaesthetic dose required is concerned, than a straight forward "number" display not indicating any trend.

As discussed above, the preferred Doppler device to be used with the present invention is a continuous wave Doppler. These are preferably cheap, easy to build and portable. In operation, the ultra sound beam is transmitted from one crystal and the reflected wave received by another. The change in frequency of the reflected signal is in part due to the velocity of the red blood cell flow. The change in the amplitude of the signal depends on the vessel, distance and tissue density differences.

Vessel wall motion alters the high amplitude, of the signals which influences the shape of the amplitude/time spectrum of the reflected wave. This problem can be minimised by using Doppler crystals with higher sound frequencies (8 to 10 MHz). In addition use of front end clutter filters designed to optimise the illumination of reflected sound from skin, subcutaneous tissue and fat can be employed, and this is preferred. Since the amplitude and time lay of the reflected noise depends on the depth and size of the blood vessel being analysed, the filters are preferably specific for either body size (e.g., adult human, child or neonate) or species (e.g., cat, dog, horse). A toggle switch preferably enables the operator to select the desired clutter filter (not shown in the figures).

The change in time difference between the reflected signal from the proximal and distal wall of the blood vessel can be analysed and will indicate changes in blood

vessel diameter. An estimate of blood vessel diameter combined with the estimate of velocity of blood flow, can be used to give index of blood flow, which can be modified in accordance with the factors discussed above to give the desired output (perfused index) which accurately correlates with Cardiac Output. As discussed in the preamble of the specification, other devices which are capable of monitoring blood flow could be used instead of continuous wave Dopplers.

As discussed above, a pulse oximeter may also be used to provide a monitoring device in accordance with the present invention.

Pulse oximeters are currently designed to measure the transmission of red and infra-red light from haemoglobin of the arterial blood and estimate the arterial oxygen saturation. However, changes in the reflective wavelength of the light from the tissue bed depend on:

A. Changes in the oxy-haemoglobin level.

B. Changes in the total mass of tissue including red blood cells.

Once a pulse oximeter is functioning on a patient, it assumes that the background tissue and blood "mass" is constant (fixed), it focuses on the pulsatile part of perfusions or blood flow wave form and therefore assumes that changes in the wavelength of the light are due to changes in oxygenation.

Typically during anaesthesia, patients breath high inspired concentrations of oxygen. Therefore, changes in light absorption are far more commonly due to changes in the mass of red blood cells (i.e., the assumed to be constant light absorption) than to changes in arterial oxygenation.

To modify a pulse oximeter, we need to work form the principle that using two light wavelengths (one in the visible red spectrum and one in the infra-red spectrum): at the isobestic wavelength, the absorbing power of oxyhaemoglobin in the reduced haemoglobin is the same.

Therefore total absorbency depends only on the sum of the two and not the state of oxygenation. Therefore the total absorbency depends only on the total amount of blood present. As tissue blood flow increases or decreases, the total absorbency at the isobestic point will change and this can be used to give a measure of the relative change in blood (mass) flow in the tissue bed. Such a device can therefore be used to monitor changes in blood flow in peripheral tissue beds.

Electromagnetic flow meters have been designed to be surgically implanted around large blood vessels such as the aorta and renal artery. It is possible that such a device may be adapted to be placed around a peripheral tissue bed, such as a finger or tail, to provide an indication of relative changes in blood flow. This may not be accurate, however.

There is no reason that an electromagnetic flow meter could not be used in the present invention, by implantation of a cuff type flow meter around a blood vessel. This is, however an invasive technique, and although it falls within the scope of the present invention it is not preferred.

Other available devices which could be adapted in accordance with the present invention are non-invasive optical flow meters. These devices measure the absorption characteristics of light scattered by blood flowing through tissues such as skin surface, detecting this reflected light, analysing the frequency of the wave forms to obtain the mean peak light frequencies in estimating blood flow. Problems with this approach are that the device only measures very superficial (i.e., skin surface) blood flow, which during anaesthesia is altered by vaso constriction such as caused by changes in body temperature. The device is also subject to movement artefacts/vibrations such as caused by patient positioning, movement by surgical manipulations, restorations, vibrations from re-circulating water beds,

etc. It is therefore difficult to get a continuous measure from a wave (pre-anaesthesia) through to anaesthesia when positioned for surgery.

Further, the signal requires considerable damping to get a stable measurement, which sacrifices the accuracy of the "real time" measurement. It also relies on estimating the Doppler signal change in the scattered light to obtain the peak frequency and fails to measure perfusion of deeper tissues. Nevertheless, although not preferred, it is quite possible that such a device could be used in the present invention.

The above description is of a relatively sophisticated device which can be used with the method in accordance with the present invention. As discussed in the preamble, a primitive device, in the form of a "colour chart" can also be used. Colours indicating various flow rates would be established by clinical trials for various species in order to produce the colour chart. An anaesthetist will then have reference to the colour chart and compare with the colour of the part of the body concerned such as the oral mucosa, in order to monitor flow rate in the subject. An example colour chart is schematically illustrated in figure 8.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

CLAIMS:

1. A method of monitoring haemodynamic function in a human or animal subject, comprising monitoring changes in blood flow in a peripheral blood vessel or tissue bed, to provide an indication of changes in cardiac output.

2. A method in accordance with claim 1, comprising the steps of monitoring relative changes in blood flow, to provide indication of relative changes in cardiac output.

3. A method in accordance with claims 1 or 2, wherein the step of monitoring blood flow is carried out non-invasively.

4. A method in accordance with claims 1, 2 or 3, wherein the step of monitoring blood flow is carried out continuously.

5. A method in accordance with any one of the preceding claims comprising the further step of setting a predetermined limit for blood flow rate, which limit indicates an alarm condition should it be reached.

6. A method in accordance with any one of claims 2 to 5, comprising the step of pre-setting a base reference level for blood flow rate being the indicated flow level of the subject at rest before monitoring of haemodynamic function, or being an average flow level for the particular type of subject prior to monitoring of haemodynamic function.

7. A method in accordance with any one of the preceding claims, wherein the step of monitoring blood flow includes employing a device which produces a signal which varies with variations in blood flow, and processing the signal to produce an output providing an indication of variations in cardiac output.

8. A method in accordance with claim 7, wherein the step of processing the signal includes the step of modifying the signal by an adjustment factor obtained by a regression analysis of a human or animal subject.

9. A method in accordance with claim 7 or 8, wherein the step of processing the signal comprises

modifying the signal by an adjustment factor obtained from a co-variate parameter.

10. A method in accordance with claim 9, wherein the co-variate parameter is heart rate.

11. A method in accordance with any one of the preceding claims, comprising the step of applying the Doppler effect to monitor blood flow.

12. A method in accordance with any one of claims 1 to 10, comprising employing an infra-red blood flow sensor (eg. pulse oximeter) to monitor blood flow.

13. A method in accordance with any one of claims 1 to 10, comprising employing an electromagnetic flow meter to monitor blood flow.

14. A method in accordance with any one of claims 1 to 10, comprising the step of employing a colour chart to monitor blood flow, and comparing the colour of a predetermined part of the subjects body with the colour chart to provide an indication of cardiac output.

15. A method in accordance with any one of claims 1 to 10, comprising the step of monitoring the colour of a part of the subjects body in order to monitor blood flow.

16. A method in accordance with any one of claims 6 to 13, wherein the signal is processed to produce a display which indicates the trend of the cardiac output.

17. A device for monitoring haemodyanmic function in a human or animal subject, comprising a blood flow monitor arranged to monitor changes in blood flow in a peripheral vessel or tissue bed, to provide an indication of changes in cardiac output.

18. A device in accordance with claim 17, wherein the blood flow monitor is arranged to monitor relative changes in blood flow, to provide an indication of relative changes in cardiac output.

19. A device in accordance with claim 17 or claim 18, further comprising a processing means for processing a signal from the blood flow monitor to produce an output signal which provides an indication of changes in cardiac

output.

20. A device in accordance with claim 19, wherein the processing means is arranged to adjust the signal by an adjustment factor obtained from regression analysis of a human or animal subject.

21. A device in accordance with claim 19 or claim 20, the processing means being arranged to adjust the signal by an adjustment factor obtained from a co-variate.

22. A device in accordance with claim 21, wherein the co-variate input is heart rate.

23. A device in accordance with any one of claims 17 to 22, wherein the blood flow monitor comprises a Doppler sensor adapted to monitor blood flow changes.

24. A device in accordance with any one of claims 17 to 22, wherein the blood flow monitor comprises an infra-red sensor such as a pulse oximeter adapted to monitor blood flow.

25. A device in accordance with any one of claims 17 to 22, wherein the blood flow monitor comprises an electromagnetic flow meter.

26. A device in accordance with any one of claims 19 to 25, comprising a display, the processing means being arranged to control the display to give an indication of changes in the cardiac output in the subject.

27. A device in accordance with claim 26, being arranged to display a base reference value to compare with an indicated value during monitoring of haemodynamic function.

28. A device in accordance with claim 26 or claim 27, being arranged to display trend analysis for changes in cardiac output, showing the trend of the changes in cardiac output.

29. A device in accordance with any one of claims 17 to 22, wherein the blood flow monitor comprises a colour chart can be compared with the colour of a predetermined part of the body of the subject.

30. A method in accordance with any one of claims 1

to 16, comprising the step of monitoring haemodynamic function in a human or animal subject during anaesthesia.

31. A method in accordance with any one of claims 1 to 16, comprising the step of monitoring haemodynamic function during critical care.

32. A method in accordance with any one of claims 1 to 16, comprising the step of monitoring haemodynamic function during stress testing.

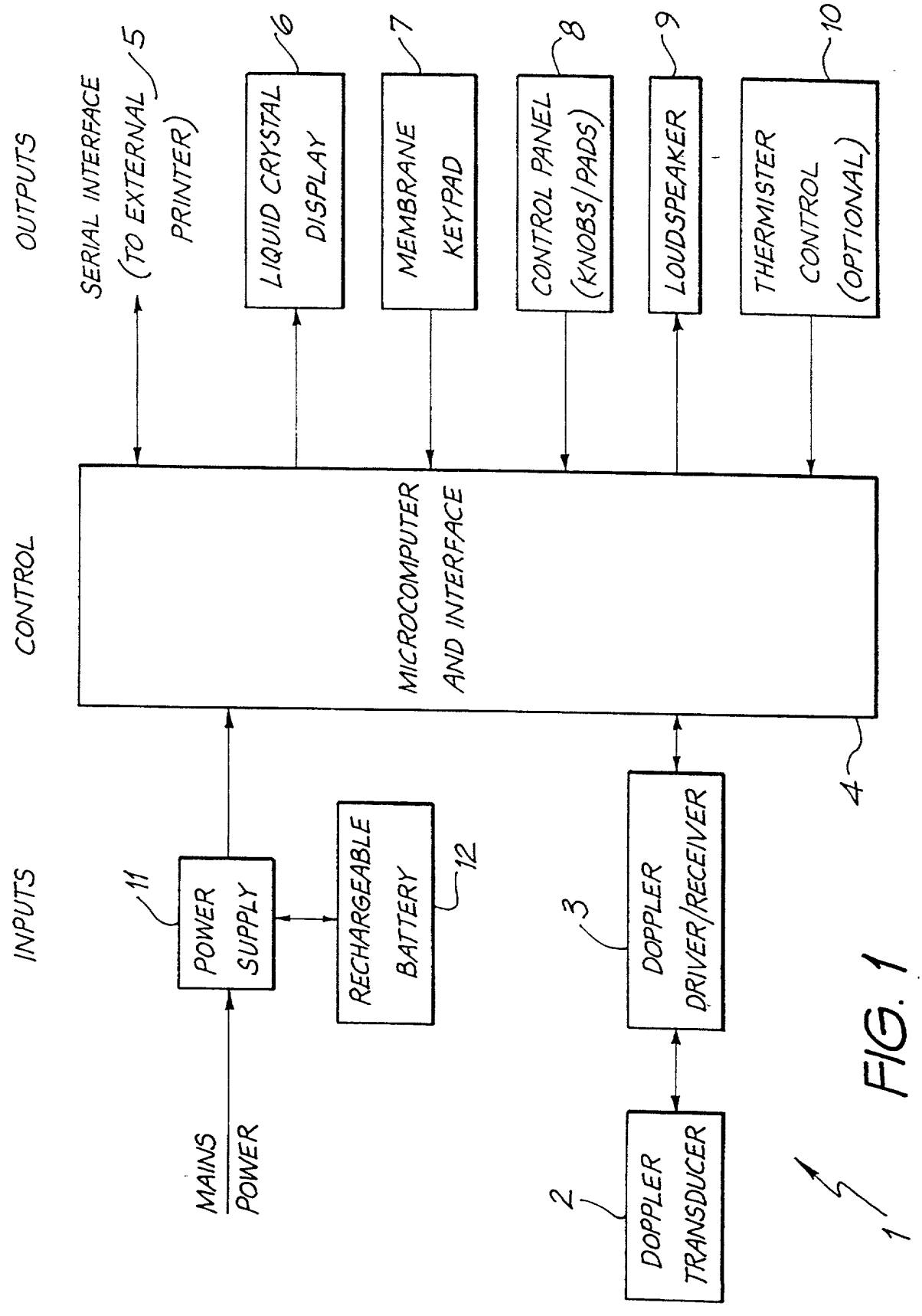
OUTPUTS
SERIAL INTERFACE (TO EXTERNAL PRINTER)
5
LIQUID CRYSTAL DISPLAY
6
MEMBRANE KEYPAD
7
CONTROL PANEL (KNOBS/PADS)
8
LOUDSPEAKER
9
THERMISTER CONTROL (OPTIONAL)
10
CONTROL
MICROCOMPUTER AND INTERFACE
4
INPUTS
11
POWER SUPPLY
RECHARGEABLE BATTERY
12
MAINS POWER
3
DOPPLER DRIVER/RECEIVER
2
DOPPLER TRANSDUCER
1

FIG. 1

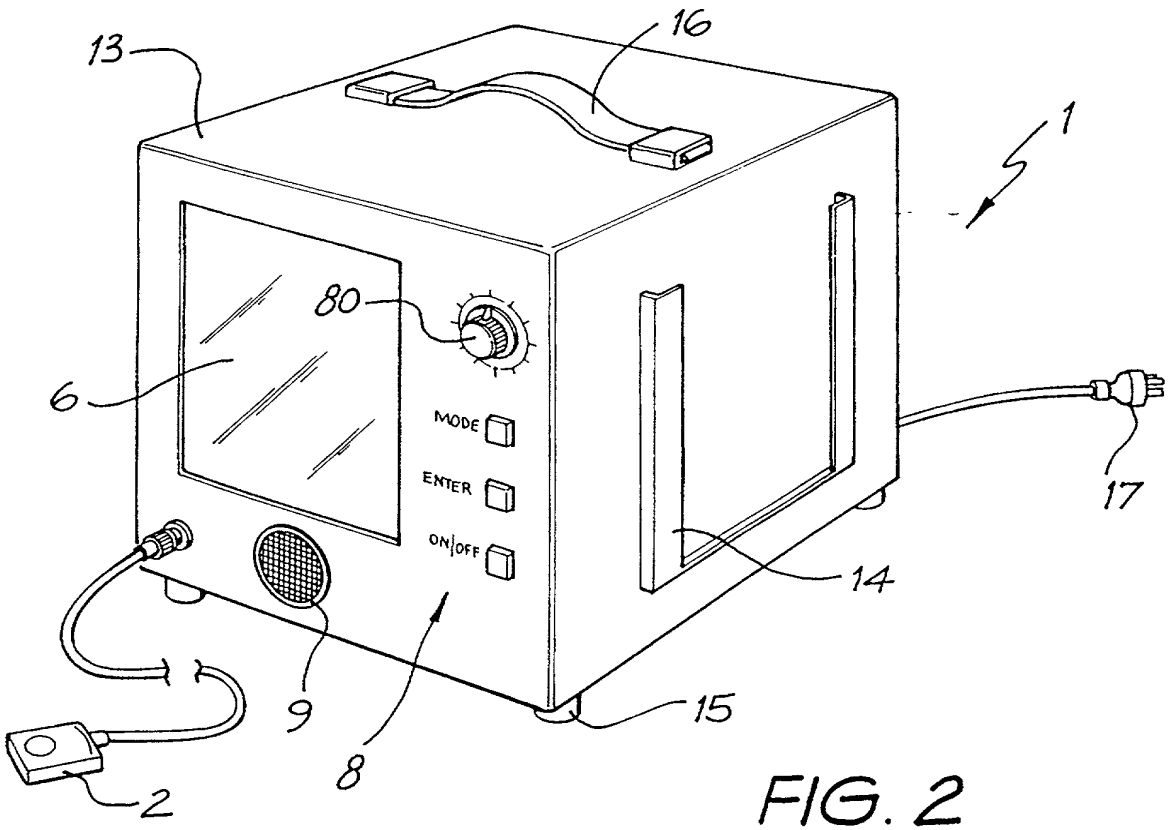
13
16
1
80
6
MODE
ENTER
ON/OFF
17
14
9
15
8
2

FIG. 2

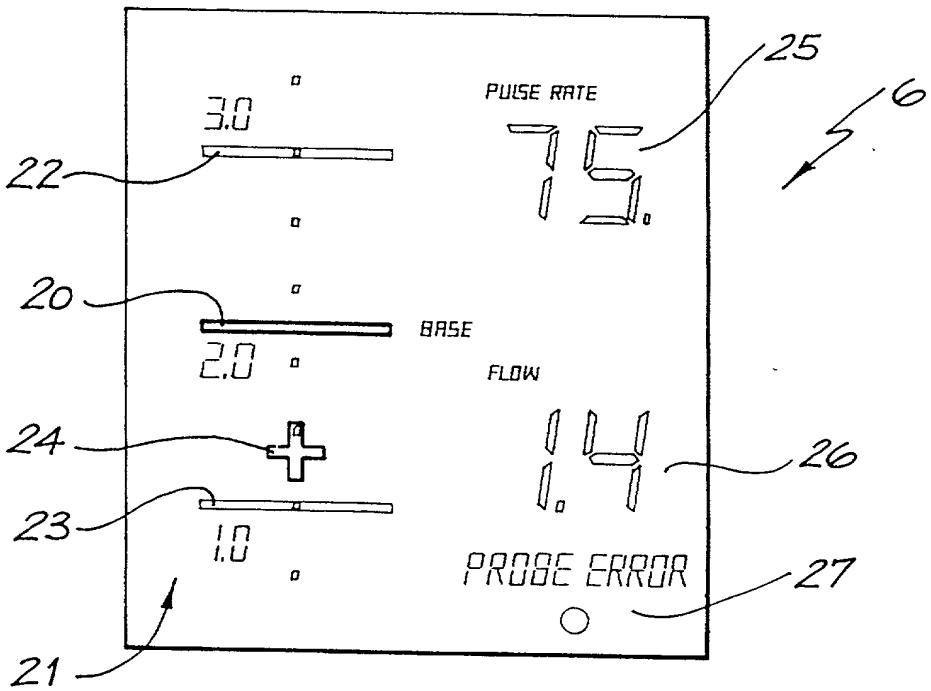
25
6
PULSE RATE
3.0
22
75.0
20
BASE
2.0
FLOW
24
14.0
26
23
1.0
PROBE ERROR
27
21

FIG. 3

DISPLAY: DATA ENTRY

PULSE	RATE	DATA
MIN	BASE	MAX
000	300	300
TONE		TONE
OFF		ON
FLOW	RATE	DATA
MIN	BASE	MAX
0.0	9.9	9.9
TONE		TONE
ON		ON

ANIMAL CLASS = NAME OR #

RUN | PAUSE | DATA | CLASS

FIG. 4

DISPLAY: DEFAULT SETTING

ANIMAL CLASS		
WEIGHT Kg	SPECIES	#
1-5	CAT/TOY DOG	1
5-10	SMALL DOG	2
10-20	MEDIUM DOG	3
20-40	LARGE DOG	4
30	SHEEP/GOAT	5
150	LLAMA/FOAL	6
450	HORSE	7

AND SLOTS FOR 'MEMORY' ? 5

RUN | PAUSE | DATA | CLASS

FIG. 5

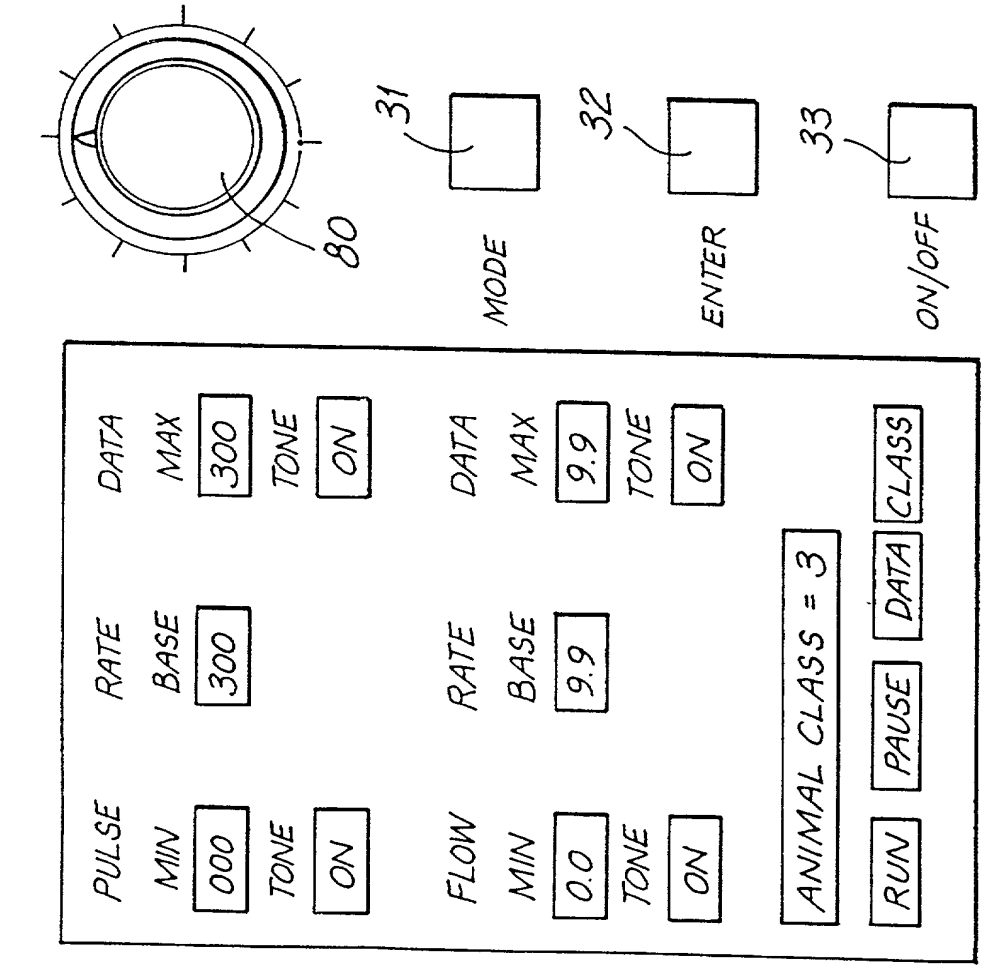
PULSE
MIN
000
TONE
ON
RATE
BASE
300
DATA
MAX
300
TONE
ON
FLOW
MIN
0.0
TONE
ON
RATE
BASE
9.9
DATA
MAX
9.9
TONE
ON
ANIMAL CLASS = 3
RUN
PAUSE
DATA
CLASS
80
31
MODE
32
ENTER
33
ON/OFF

FIG. 6

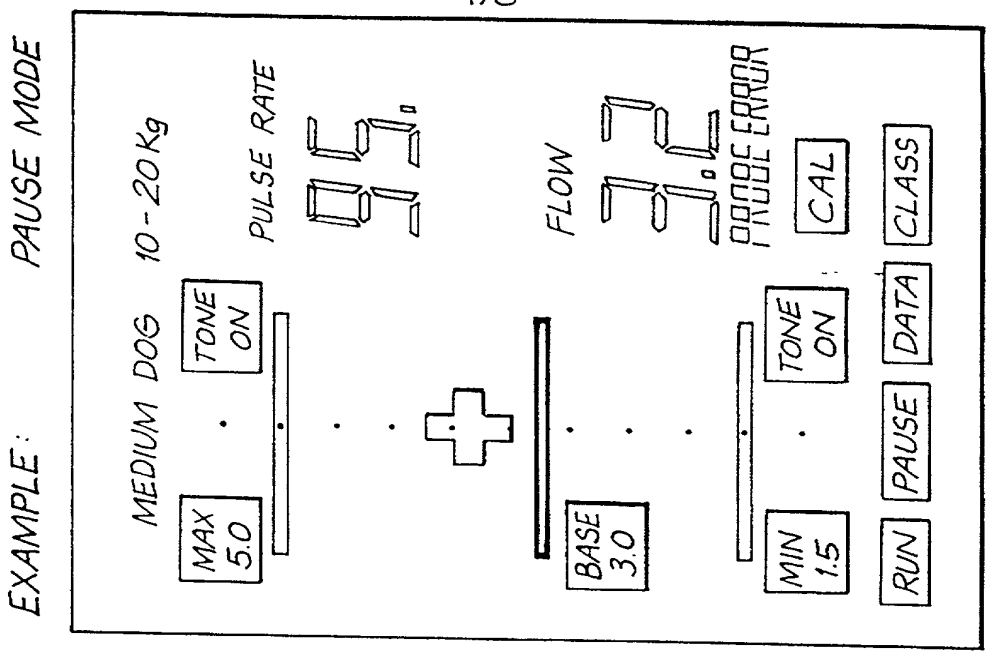
EXAMPLE:
PAUSE MODE
MEDIUM DOG 10 - 20 Kg
MAX 5.0
TONE ON
PULSE RATE
65
FLOW
3.2
PROBE ERROR
BASE 3.0
MIN 1.5
TONE ON
CAL
RUN
PAUSE
DATA
CLASS

FIG. 7

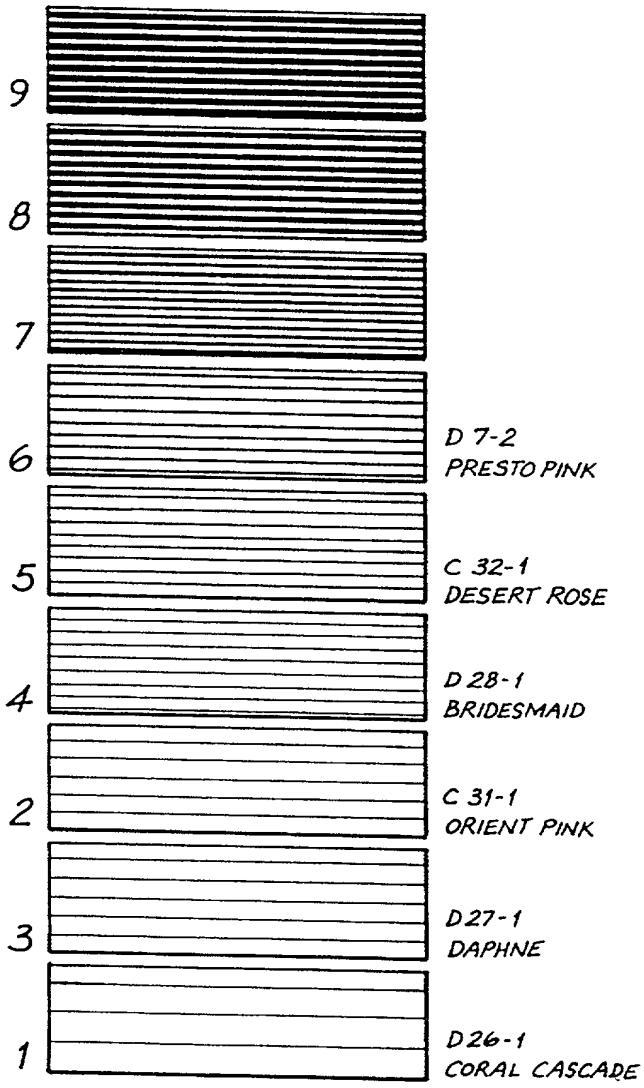
9
8
7
6
D 7-2
PRESTO PINK
5
C 32-1
DESERT ROSE
4
D 28-1
BRIDESMAID
2
C 31-1
ORIENT PINK
3
D 27-1
DAPHNE
1
D 26-1
CORAL CASCADE

FIG. 8

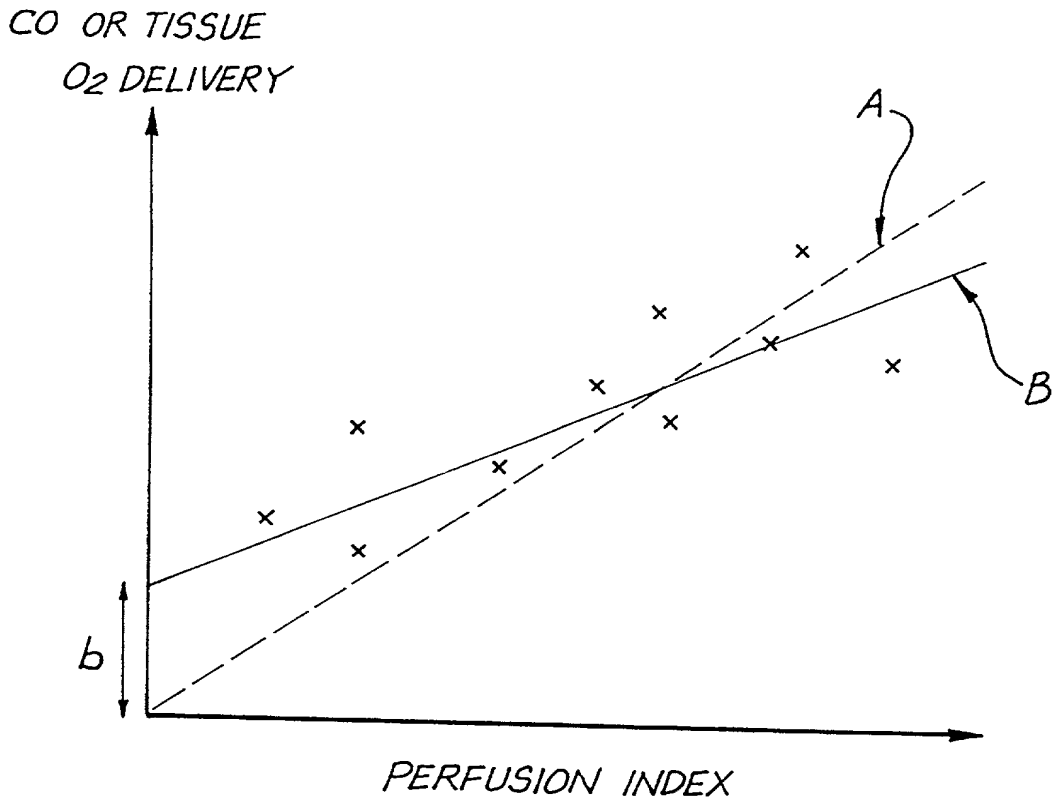

FIG. 9

GRIHAC P26AUS

COMBINED DECLARATION AND POWER OF ATTORNEY

(Original, Design, National Stage of PCT, Supplemental)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: (check one applicable item below)

- ☐ original
- ☐ design
- ☐ supplemental
- ■ National Stage of PCT
- ☐ divisional (see added page)
- ☐ continuation (see added page)
- ☐ continuation-in-part (see added page)

INVENTORSHIP IDENTIFICATION

My/our residence, post office address and citizenship is/are as stated below next to my/our name. I/We believe that the named inventor or inventors listed below is/are the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

METHOD AND APPARATUS FOR MONITORING HAEMODYNAMIC FUNCTION

SPECIFICATION IDENTIFICATION

The specification of which: (complete (a), (b) or (c))

(a) ☐ is attached hereto.

(b) ☐ was filed on with an effective filing date of May 13, 1998 as
☐ Serial No. 09/423,776 or
☐ Express Mail No. _____ as Serial No. (not yet known) and was amended on _____ (if applicable).

(c) ■ was described and claimed in PCT International Application No. PCT/AU98/00356 filed on 13 May 1998 and as amended under PCT Article 19 on _____ (if any).

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name(s) and registration number(s))

Anthony G. M. Davis	Registration No. 27,868
Michael J. Bujold	Registration No. 32,018
Scott A. Daniels	Registration No. 42,462

☐ Attached as part of this Declaration and Power of Attorney is the authorization of the above-named attorney(s) to accept and follow instructions from my representative(s).

Send Correspondence to:

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Direct Telephone Calls to:
(603) 624-9220

Direct Telefaxes to:
(603) 624-9229

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I/We hereby state that I/we have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I/We acknowledge the duty to disclose to the United States Patent Office all information which is known to be material to patentability of this application as defined in § 1.56 of Title 37 of the Code of Federal Regulations.

PRIORITY CLAIM

I/We hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me/us on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

COUNTRY	APPLICATION NO.	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 37 USC 119
Australia	PO6763	13 May 1997	■YES □NO
			□YES □NO
			□YES □NO
			□YES □NO
			□YES □NO

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

_____

_____

□ I/We hereby claim the benefit, under 35 U.S.C. 119(e), of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YY)	□ Additional provisional application numbers are listed on a supple-mental priority data sheet PTO/SB/02B attached hereto.

DECLARATION

I/We hereby declare that all statements made herein of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1 – 00

Full name of sole inventor: Colin DUNLOP

Inventor's signature:  Date: JANUARY 5, 2000

Residence: 132A Cressy Road, East Ryde NSW 2113, Australia AUX

Post Office Address: Same as above Country of Citizenship: Australia